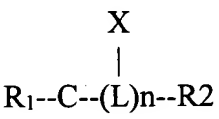
is defective because the filing date for application Serial No. 08/504,856 incorrectly indicated June 20, 1995 as the filing date. As discussed with the Examiner in a telephone conference on October 29, 2001, the applicants will submit a Supplementary Declaration correctly indicating the filing date of application Serial No. 08/504,856 as July 20, 1995 after a Notice of Allowance is issued.

The applicants acknowledge the Examiner's objections to the drawings as noted on form PTO 948 and enclose herewith six (6) sheets of formal drawings in compliance with 37 C.F.R. § 1.84.

The Examiner rejects claims 1, 10, 11, 17, and 18 under 35 USC §102(b) as being anticipated by Fluo-GRP™, stating the applicants disclosed the existence of a fluorescently labeled gastrin-releasing peptide introduced by the assignee, Advanced Bioconcept Ltd.

The applicants respectfully disagree with the Examiner that Fluo-GRP™ discloses each and every element of the applicants claimed invention. The unique compound as claimed by the applicants comprises a compound of the formula:



wherein $R_1$ is a light-emitting moiety and $R_2$ is a bombesin-like peptide, fragment, derivative or analog thereof, and L is a linker moiety, wherein n is 1 or 0, and (C-X) is selected from the group consisting of C=O, C=S, CH(OH), C=C=O, C=NH, $CH_2$, CH(OR), CH(NR), CH(R), $CR_3R_4$, and $C(OR_3)OR_4$ where R, $R_3$, and $R_4$ are alkyl moieties or substituted alkyl moieties, and wherein (L)n--$R_2$ is linked to (C-X) at L or at an amino acid position selected such that the compound exhibits substantial biological activity in the presence of a receptor having an affinity for bombesin-like peptides.

As elected and acknowledged by the Examiner, the compound as claimed by the



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applicants includes the light-emitting moiety BODIPY, a carbon oxygen linkage, and gastrin-releasing protein. In sharp contrast, Fluo-GRP™ discloses the light-emitting moiety fluorescein. BODIPY and fluorescein are different light emitting moieties with different light emitting characteristics. Therefore, Fluo-GRP™ does not a disclose, teach, or suggest a gastrin-releasing peptide with the light emitting moiety BODIPY as claimed by the applicants in claim 1. Because Fluo-GRP™ does not disclose each and every element of the applicants' claimed invention, namely the light emitting moiety BODIPY, the Examiner's rejection under 35 U.S.C. §102(b) should be withdrawn.

Accordingly, independent claim 1 is clearly allowable and patentable under 35 U.S.C. §102(b). Because claims 10, 11, 17, and 18 depend on an allowable base claim, claims 10, 11, 17, and 18 are clearly patentable under 35 U.S.C. §102(b).

The Examiner rejects claims 1, 3, 5-8, and 10-27 under 35 USC §103(a) as being unpatentable over EPA 606 804 ('804) in view of the Bunnett et al. publication "Characterization of Receptors Using Cyanine 3-Labeled Neuropeptides." The Examiner contends that EPA '804 teaches a fluorescent compound and method of making thereof which is useful in flow cytometric studies, cell sorting and receptor-labeling experiments. The Examiner states the compound as taught by '804 comprises a fluorophore ($R_1$) selected from the group consisting of fluorescein, rhodamine, blue fluorescent and BODIPY, a carbon=oxygen linkage, and a polypeptide moiety (R) which is disclosed as being a neurotensin analog. The Examiner admits, however, that EPA '804 does not disclose that the polypeptide moiety is a gastrin releasing peptide (GRP) as claimed by the applicants, and looks to Bunnett which teaches a cyanine labeled GRP which may be used in receptor localization or flow analysis and cell sorting. The Examiner contends that it would have been obvious to one of ordinary skill in the art to modify the compound of EPA '804 by linking the cyanine labeled GRP of Bunnett to the

fluorophores, namely, BODIPY of EPA '804, not only because fluorescently labeled GRP is known in the art, as shown Bunnett, but also because EPA '804 raises the "expectation of success" by disclosing that conjugating the neurotensin peptide to the fluorophore through a carbon=oxygen bond results in a compound that retains the "pharmacological" or functional properties that are found in native peptides, thus producing a compound that is a non-toxic highly sensitive marker for identifying receptors of interest.

The applicants respectfully disagree with the Examiner that the combination of EPA '804 and Bunnett teach what the applicants claim. The applicants and the Examiner agree "EPA '804 does not disclose that the polypeptide peptide moiety is a gastrin-releasing peptide (GRP) as claimed by the Applicant[s]" (see page 4 of the July 31, 2001 Office Action). But, in addition, EPA '804 does not provide any expectation that light-emitting compounds containing a light-emitting moiety should be combined with a gastrin-releasing peptide which will exhibit substantial biological activity in the presence of a receptor having affinity for gastrin-releasing peptides, and where the light-emitting moiety and peptide are linked via a -(C-X)- group (where C-X is C=O), as claimed by applicants in claim 1.

Further, EPA '804 and Bunnett do not disclose, teach, or suggest selecting the light-emitting compound having substantial biological activity in the presence of a receptor having affinity for a gastrin-releasing peptides from a mixture including secondary compounds that have biological activities less than 0.25% of the biological activity of the gastrin-releasing peptide, as claimed by the applicants in claim 22.

Moreover, receptor-peptide recognition interaction relies on substantially maintaining the binding domain of the peptide. It is a goal of EPA '804 to maintain the binding specificity of neurotensin to neurotensin receptors, while it is the goal of the applicants' claimed invention to maintain the binding specificity of gastrin-releasing peptides to gastrin-releasing peptide

receptors. One of these results certainly does not suggest the other, since any structural modification of a peptide can significantly affect the binding affinity of a receptor to that peptide. Therefore, EPA '804 actually teaches away from the applicants claimed invention rather than suggesting it.

The effect of structural modification (i.e., by attaching a light-emitting moiety) to a peptide can affect each peptide in a different and unpredictable manner that depends upon the type of modification and the location of the modification on the peptide. For example, the structure of the binding domain of labeled neurotensin of EPA '804 includes the sequence -Arg-Arg-Pro-(Tyr or Trp)-Ile-Leu. See page 5, lines 1-36 or claim 1 of EPA '804. In sharp contrast, the applicants claims 5 recites the structure of the binding domain of the labeled gastrin-releasing protein comprising the sequence Val-Pro-Leu-Pro-Ala-Gly-Gly-Gly-Thr-Val-Leu-Thr-Lys-Met-Tyr-Pro-Arg-Gly-Asn-His-Trp-Ala-Val-Gly-His-Leu-Met. The region of interest for receptor binding of the peptides as disclosed in EPA '804 and the applicants claimed invention, therefore, has a different amino acid sequence which is consistent with the fact that each of the peptides selectively binds to different receptors. Since the binding domains of EPA '804 and those of the applicants claimed invention are significantly different, a modification that produces a functional neurotensin peptide as taught by EPA '804 will not predictably result in the production of a biologically active light-emitting gastrin-releasing peptide as claimed by the applicants in claims 1 and 5.

In addition, the linkages as disclosed in EPA '804 will not predictably extend the observed binding specificities from neurotensin to gastrin-releasing peptide as claimed by the applicants, or any other peptide, when the binding ability of the peptide to its specific receptor is essential to its function. Nowhere in the entire disclosure of EPA '804 is the suggestion that carbonyl or thiocarbonyl linkages that are appropriate for linking a fluorophore to neurotensin

may be extrapolated to include linking light-emitting moieties to other peptides, particularly peptides that bind to gastrin-releasing proteins receptors as claimed by the applicants.

Therefore, EPA '804 does not disclose, teach, or suggest the applicants' claimed compound which exhibits substantial biological activity in the presence of a receptor having affinity for gastrin-releasing proteins.

Further, EPA '804 does not disclose, teach, or suggest selecting the light-emitting compound, including a particular peptide sequence that has substantial biological activity in the presence of a receptor having affinity for the peptide sequence from a mixture including secondary compounds that have biological activities less than 0.25% of the biological activity of the gastrin-releasing protein, as claimed by the applicants in claim 22. In EPA '804, the neurotensin analogue is labeled and the labeled compound is purified by solid phase techniques, resulting in a single modified compound. See page 7, line 36 – page 8, line 4 of EPA '804. In the acquisition of the gastrin-releasing protein of the light-emitting compound as claimed by the applicants, the light-emitting compound with substantial biological activity is selected from the "relatively inactive fluorescent peptides." See applicants' specification, page 15, lines 6-13. This key selection step is not suggested, taught, or disclosed in EPA '804.

Finally, as known in the art, the mere fact that a peptide can be labeled with a light-emitting moiety does not suggest that the product is a light-emitting compound or a light-emitting compound having substantial biological activity. For example, even if a light-emitting moiety is chemically linked to a peptide, the fluorescence of the light-emitting moiety can be quenched (i.e., a light-emitting compound is not obtained with certainty). Moreover, even if the light-emitting moiety is chemically linked to a peptide and fluorescence of the light-emitting moiety is not quenched, the biological activity of the light-emitting compound can vary widely.

With regard to the secondary reference cited by the Examiner, Bunnett teaches the

labeling GRP with red fluorophore cyanin 3.18 (cy3). Red fluorophore cyanine 3.18 is a "very bright fluorophore which is resistant to photobleaching and is not quenched" (see Bunnett, page 733, column 2, paragraph 2). In sharp contrast, the applicants claim a light-emitting compound with substantial biological activity that is selected from the "relatively inactive fluorescent peptides", such as BODIPY (see applicants' specification, page 15, lines 6 - 13). Therefore, Bunnett actually teaches away from the applicants' claimed invention. Further, there is no teaching, suggestion or disclosure in Bunnett of any way of selecting such a compound from a mixture that includes compounds with relatively low biological activities. See applicants' claims 1 and 22.

As shown above, neither EPA '804 nor Bunnett, alone or in combination, disclose, teach, or suggest a light-emitting moiety BODIPY, a carbon oxygen linkage, an a gastrin-releasing protein wherein the compound exhibits substantial biological activity in the presence of a receptor having affinity for gastrin-releasing protein, as claimed by the applicants in independent claim 1.

Therefore, the proposed combination of EPA '804 and Bunnett fails to disclose, teach, or suggest each and every element of the applicants' claimed invention. Accordingly, claim 1 is clearly patentable under 35 USC §103(a). Because claims 3, 5-8, and 10-27 depend from an allowable base claim, claims 3, 5-8, and 10-27 are allowable and patentable under 35 USC §103(a).

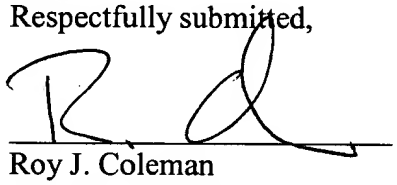
Further, the proposed combination of EPA '804 and Bunnett fails to disclose, teach, or suggest the structure of the binding domain of the labeled gastrin-releasing protein comprising the sequence Val-Pro-Leu-Pro-Ala-Gly-Gly-Gly-Thr-Val-Leu-Thr-Lys-Met-Tyr-Pro-Arg-Gly-Asn-His-Trp-Ala-Val-Gly-His-Leu-Met as claimed by the applicants in claim 5. Therefore, the rejection of claim 5 under 35 USC §103(a) is improper.

Finally, the proposed combination of EPA '804 and Bunnett fails to disclose, teach or suggest selecting the light-emitting compound having substantial biological activity in the presence of a receptor having affinity for gastrin-releasing protein from a mixture including secondary compounds that have biological activities less than 0.25% of the biological activity of the gastrin-releasing peptide, as claimed by the applicants in claim 22. Therefore, the rejection of claim 22 under 35 USC §103(a) is improper. Because claims 23 and 24 depend from claim 22, the rejection of claims 23 and 24 under §103(a) is also improper.

Each of the Examiner's rejections has been addressed or traversed. Accordingly, it is respectfully submitted that the application is in condition for allowance. Early and favorable action is respectfully requested.

If for any reason this Response is found to be incomplete, or if at any time it appears that a telephone conference with counsel would help advance prosecution, please telephone the undersigned or his associates, collect in Waltham, Massachusetts, at (781) 890-5678.

Respectfully submitted,



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